REMARKS

This Amendment responds to the final office action mailed October 2, 2007 (the Office Action). The Office Action was carefully reviewed.

Status of the Claims

Claims 1-10, 13-25, 27, 29-41, 43-57 and 59-64 are pending. Claims 17-25, 27, 29-38, and 62 are under examination. Previously withdrawn claims 1-10, 13-16, 39-41, 43-57, and 59-64 are cancelled herein. Claims 18, 20, 25 and 27 are cancelled and claim 17 is amended.

Claims 17 was amended to include the limitations of claim 18 (rectum and prostate). Claim 17 was also amended to recite an injectable material (e.g., as at page 12, line 23) that is a gel in the body (e.g., as at page 7 line 21.

New claim 65 is added, with the claim being the claim described as allowable in the Office Action.

Amendments to the specification

The specification has been amended to include certain material incorporated by reference. The first amendment to the specification (numbered "1") is a copy of disclosure from columns 7-10 of U.S. Pat. No. 6,129,761 entitled "Injectable Hydrogel Compositions" which was incorporated by reference at page 8 line 16. The copied text has been adapted for grammar and context. No new matter is added. Please see Appendix I.

The second amendment to the specification (numbered "2") is a copy of disclosure from columns 4-5 of U.S. Pat. No. 5,599,552 entitled "Biodegradable Polymer Composition" which was incorporated by reference at page 8 line 16. The copied text has been adapted for grammar and context. No new matter is added. Please see Appendix II.

First rejection for lack of enablement

Claims 17-25, 27, 29-38, and 62-64 were rejected under 35 U.S.C. §112 ¶1 on the grounds of nonenablement for a first tissue location other than "rectum". Applicant respectfully disagrees but has amended the claims to facilitate prosecution.

Second rejection for lack of enablement

Claims 17-25, 27, 29-38, and 62-64 were rejected under 35 U.S.C. §112 ¶1 on the grounds of nonenablement for materials other than collagen. The Office Action argues that Applicant has only established ample support for collagen, as at pages 5-6, with support for other embodiments being generally lacking. The Office Action looks to page 6, lines 7-9 and finds that the disclosure that "Other materials may be used [etc.]" is not adequate.

In general, the Applicant has performed detailed investigations in humans that prove that the claimed biocompatible, biodegradable, injectable gels may be used as claimed. Collagen is one such material that is available; the techniques used for collagen may readily be adapted for use with other materials available to the artisan and described at length in the specification. The specification provides various biocompatible, biodegradable, injectable gel fillers that are set forth at length and in detail at, e.g, page 7 line 20 to pages 8 line 18, page 10 lines 4-13, and page 11 lines 5-22. Now that the Applicant has proven that collagen can be used, it is logical that other biocompatible, biodegradable, injectable gel materials can also be used.

Nonetheless, the specification has been amended to include further detail drawn from the references incorporated by reference that provide details on filler materials uses, properties, and preparation. Therefore the Examiner is requested to withdraw this rejection. Further analysis is presented below.

MPEP 2164.01 describes the test for enablement as follows. Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of

whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable. MPEP 2164.01(a) describes the Wands factors for undue experimentation.

MPEP 6164.04 describes the Patent Office's burden as follows. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In the present case, it is respectfully submitted that the Patent Office has not carried its burden since the Office Action points to support in the specification but provides no explanation as to why this support is not enabling. Respectfully, such an approach is not adequate for the Patent Office to make-out a valid rejection. As explained below, however, artisans that read the application will be able to practice what is claimed without undue experimentation.

The specification does support and enable what is claimed. Referring to amended claim 17 (wherein the filler device is introduced as an expandable sponge or an injectable material), as explained on page 6 of the Application (lines 6-10), "The successful use of collagen as a filler shows that other materials may also be used. Other materials may include natural or synthetic

materials, e.g., proteins, extracellular matrix molecules, fibrin, proteins, hyaluronic acid, albumin, bulking agents, and polyethylene glycol-based materials". And "A filler is a substance that occupies a volume after its introduction into a body. Examples of fillers include but are not limited to polymers, gels, sols, hydrogels, sponges, bulking agents, and balloons. Filler materials include polysaccharides, alginate, collagen, gelatin, fibrin, fibrinogen, albumin, serum, autologous serum, sutures, and natural and synthetic polymers. Synthetic polymers include polylactide, polyglycolide, polycaprolactones, poly(alpha.-hydroxy acid), poly(amino acid), and poly(anhydride). Fillers may be crosslinked or uncrosslinked. Polymers include polyethylene glycol and derivatives thereof, including crosslinked polyethylene glycols. Other types of polymers include thermoreversible and thixotropic polymers. Other examples of a filler include self-absorbing suture material held within a suspension (such as prolene sutures)", see specification page 7 line 20-page 8 line 7.

Fillers from commercial sources are disclosed in the specification at pages 11-21: "Other examples of fillers are hyaluronic acid, cellulose, alginate, and gelatin, which are available from commercial sources, e.g., Sigma-Aldrich, Inc. and ICN Biomedicals, Inc. Hyaluronic acid is a material that is accepted in the medical community as a material that may be implanted into a patient; other commercial sources are Genzyme Advanced Biomaterials (e.g., HyluMed®), LifeCore Biomedical, and FMC BioPolymer. Another example of a filler is cellulose, e.g., Avicel® a thixotropic cellulose product from FMC BioPolymer. Another filler example is synthetic polymer hydrogels, e.g., as made by Angiotech Pharmaceuticals, e.g., Coseal®. Other fillers are described in, e.g., U.S. Patent No. 6,224,893, and other references set forth herein.

The Office action pointed particularly to "polyethylene glycol" as not being enabled. The passage just quoted refers to Coseal®, a polyethylene glycol-material (see attached Coseal® literature, 2 documents). Further, material incorporated by reference and copied into the specification describes "For example, a mixture of polyethylene oxide and polyacrylic acid

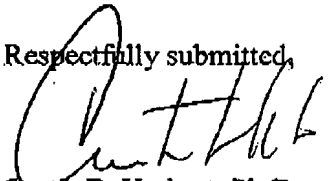
which gels by hydrogen bonding upon mixing may be utilized" and "PEG-oligolactyl-acrylates", "polyalkylene oxalates", and "polyalkylene succinates" are described, with a polyethylene glycol being a well-known type of polyalkylene.

Accordingly, the artisan may follow the working examples or the specification to make a degradable device as claimed using various fillers. The fillers that are disclosed include more than 20 specific embodiments that may be obtained using methods detailed in the literature or merely by ordering products that are commercially available. Therefore it is not undue experimentation to make and practice what is claimed.

Request for allowance

Allowance of the claims is requested. The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,



Curtis B. Herbert, Ph.D.
Registration No. 45,443

Customer No. 62274
Dardi & Associates, PLLC
US Bank Plaza, Suite 2000
220 South 6th Street
Minneapolis, Minnesota 55402
Telephone: (612) 605-1038

APPENDIX I: Comparison of text for the first amendment to the specification (numbered "1") as a copy of disclosure from columns 7-10 of U.S. Pat. No. 6,129,761 entitled "Injectable Hydrogel Compositions". The original text from U.S. Pat. No. 6,129,761 is presented below, with changes shown in strikethrough or underline.

Polymeric materials which are capable of forming a hydrogel ~~are~~ may be utilized. ~~The polymer is mixed with cells for implantation into the body and is permitted to crosslink to form a hydrogel matrix containing the cells either before or after implantation in the body.~~ In one embodiment, the polymer forms a hydrogel within the body upon contact with a crosslinking agent. A hydrogel is defined as a substance formed when an organic polymer (natural or synthetic) is crosslinked via covalent, ionic, or hydrogen bonds to create a three-dimensional open-lattice structure which entraps water molecules to form a gel. Naturally occurring and synthetic hydrogel forming polymers, polymer mixtures and copolymers may be utilized as hydrogel precursors.

Examples of materials which can be used to form a hydrogel include modified alginates. Alginate is a carbohydrate polymer isolated from seaweed, which can be crosslinked to form a hydrogel by exposure to a divalent cation such as calcium, as described, for example in WO 94/25080~~, the disclosure of which is incorporated herein by reference. The modified alginate solution is mixed with the cells to be implanted to form a suspension. Then the suspension is injected directly into a patient prior to crosslinking of the polymer to form the hydrogel containing the cells. The suspension then forms a hydrogel over a short period of time due to the presence in vivo of physiological concentrations of calcium ions.~~ [¶] Alginate is ionically crosslinked in the presence of divalent cations, in water, at room temperature, to form a hydrogel matrix. ~~Due to these mild conditions, alginate has been the most commonly used polymer for hybridoma cell encapsulation, as described, for example, in U.S. Pat. No. 4,352,883 to Lim. In the Lim process, an aqueous solution containing the biological materials to be encapsulated is suspended in a solution of a water soluble polymer, the suspension is formed into droplets which are configured into discrete microcapsules by contact with multivalent cations, then the surface of the microcapsules is crosslinked with polyamino acids to form a semipermeable membrane around the encapsulated materials.~~ [¶] Modified alginate derivatives may be synthesized which have an improved ability to form hydrogels. The use of alginate as the starting material is advantageous because it is available from more than one source, and is available in good purity and characterization. As used herein, the term "modified alginates" refers to chemically modified alginates with modified hydrogel properties. Naturally occurring alginate may be chemical modified to produce alginate polymer derivatives that degrade more quickly. For example, alginate may be chemically cleaved to produce smaller blocks of gellable oligosaccharide blocks and a linear copolymer may be formed with another preselected moiety, e.g. lactic acid or .epsilon.-caprolactone. The resulting polymer includes alginate blocks which permit ionically catalyzed gelling, and oligoester blocks which produce more rapid degradation depending on the synthetic design. Alternatively, alginate polymers may be used, wherein the ratio of mannuronic acid to guluronic acid does not produce

a firm gel, which are derivatized with hydrophobic, water-labile chains, e.g., oligomers of .epsilon.-caprolactone. The hydrophobic interactions induce gelation, until they degrade in the body.

Additionally, polysaccharides which gel by exposure to monovalent cations, including bacterial polysaccharides, such as gellan gum, and plant polysaccharides, such as carrageenans, may be crosslinked to form a hydrogel using methods analogous to those available for the crosslinking of alginates described above. Polysaccharides which gel in the presence of monovalent cations form hydrogels upon exposure, for example, to a solution comprising physiological levels of sodium. Hydrogel precursor solutions also may be osmotically adjusted with a nonion, such as mannitol, and then injected to form a gel.

Polysaccharides that are very viscous liquids or are thixotropic, and form a gel over time by the slow evolution of structure, are also useful. For example, hyaluronic acid, which forms an injectable gel with a consistency like a hair gel, may be utilized. Modified hyaluronic acid derivatives are particularly useful. As used herein, the term "modified hyaluronic acids" refers to chemically modified hyaluronic acids. Modified hyaluronic acids may be designed and synthesized with preselected chemical modifications to adjust the rate and degree of crosslinking and biodegradation. For example, modified hyaluronic acids may be designed and synthesized which are esterified with a relatively hydrophobic group such as propionic acid or benzylic acid to render the polymer more hydrophobic and gel-forming, or which are grafted with amines to promote electrostatic self-assembly. Modified hyaluronic acids thus may be synthesized which are injectable, in that they flow under stress, but maintain a gel-like structure when not under stress. Hyaluronic acid and hyaluronic derivatives are available from Genzyme, Cambridge, Mass. and Fidia, Italy.

Other polymeric hydrogel precursors include polyethylene oxide-polypropylene glycol block copolymers such as Pluronics [[tm]] or Tetronics [[tm]] which are crosslinked by hydrogen bonding and/or by a temperature change, as described in Steinleitner et al., Obstetrics & Gynecology, 77:48-52 (1991); and Steinleitner et al., Fertility and Sterility, 57:305-308 (1992). ¶ Other materials which may be utilized include proteins such as fibrin, collagen and gelatin. Polymer mixtures also may be utilized. For example, a mixture of polyethylene oxide and polyacrylic acid which gels by hydrogen bonding upon mixing may be utilized. In one embodiment, a mixture of a 5% w/w solution of polyacrylic acid with a 5% w/w polyethylene oxide (polyethylene glycol, polyoxyethylene) 100,000 can be combined to form a gel over the course of time, e.g., as quickly as within a few seconds.

Covalently crosslinkable hydrogel precursors also are useful. For example, a water soluble polyamine, such as chitosan, can be cross-linked with a water soluble diisothiocyanate, such as polyethylene glycol diisothiocyanate. The isothiocyanates will react with the amines to form a chemically crosslinked gel. Aldehyde reactions with amines, e.g., with polyethylene glycol dialdehyde also may be utilized. A hydroxylated water soluble polymer also may be utilized.

Alternatively, polymers may be utilized which include substituents which are crosslinked by a radical reaction upon contact with a radical initiator. For example, polymers including ethylenically unsaturated groups which can be photochemically crosslinked may be utilized, as disclosed in WO 93/17669~~, the disclosure of which is incorporated herein by reference~~. In this embodiment, water soluble macromers that include at least one water soluble region, a biodegradable region, and at least two free radical-polymerizable regions, are provided. The macromers are polymerized by exposure of the polymerizable regions to free radicals generated, for example, by photosensitive chemicals and or light. Examples of these macromers are PEG-oligolactyl-acrylates, wherein the acrylate groups are polymerized using radical initiating systems, such as an eosin dye, or by brief exposure to ultraviolet or visible light. Additionally, water soluble polymers which include cinnamoyl groups which may be photochemically crosslinked may be utilized, as disclosed in Matsuda et al., ASAID Trans., 38:154-157 (1992).

~~In general, the polymers are at least partially soluble in aqueous solutions, such as water, buffered salt solutions, or aqueous alcohol solutions. Methods for the synthesis of the other polymers described above are known to those skilled in the art. See, for example Concise Encyclopedia of Polymer Science and Polymeric Amines and Ammonium Salts, E. Goethals, editor (Pergamon Press, Elmsford, N.Y. 1980). Many polymers, such as poly(acrylic acid), are commercially available. Naturally occurring and synthetic polymers may be modified using chemical reactions available in the art and described, for example, in March, "Advanced Organic Chemistry," 4th Edition, 1992, Wiley-Interscience Publication, New York.~~

Water soluble polymers with charged side groups may be crosslinked by reacting the polymer with an aqueous solution containing ions of the opposite charge, either cations if the polymer has acidic side groups or anions if the polymer has basic side groups. Examples of cations for crosslinking of the polymers with acidic side groups to form a hydrogel are monovalent cations such as sodium, and multivalent cations such as copper, calcium, aluminum, magnesium, strontium, barium, and tin, and di-, tri- or tetra-functional organic cations such as alkylammonium salts. Aqueous solutions of the salts of these cations are added to the polymers to form soft, highly swollen hydrogels and membranes. The higher the concentration of cation, or the higher the valence, the greater the degree of cross-linking of the polymer. Additionally, the polymers may be crosslinked enzymatically, e.g., fibrin with thrombin.

APPENDIX II: Comparison of text for the second amendment to the specification (numbered "2") as a copy of disclosure from columns 4-5 of U.S. Pat. No. 5,599,552 entitled "Biodegradable Polymer Composition". The original text from U.S. Pat. No. 5,599,552 is presented below, with changes shown in strikethrough or underline.

~~Thermoplastic polymer composition~~

Thermoplastic polymers ~~useful in the composition of the invention~~ include pharmaceutically compatible polymers that are bioerodible by cellular action, are biodegradable by action of non-living body fluid components, soften when exposed to heat but return to the original state when cooled and are capable of substantially dissolving or dispersing in a water-miscible carrier or solvent to form a solution or dispersion. Upon contact with an aqueous fluid and the dissipation of the solvent component, the thermoplastic polymers are capable of coagulating or solidifying to form a solid or gelatinous matrix suitable for use as an implant in an animal. [[¶]] The kinds of thermoplastic polymers suitable for the present composition generally include any having the foregoing characteristics. Examples are polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein. Polylactides, polycaprolactones, polyglycolides and copolymers thereof are highly preferred thermoplastic polymers.

The thermoplastic polymer is combined with a suitable organic solvent to form a solution. The solubility or miscibility of a polymer in a particular solvent will vary according to factors such as crystallinity, hydrophilicity, capacity for hydrogen-bonding and molecular weight of the polymer. Consequently, the molecular weight and the concentration of the polymer in the solvent are adjusted to achieve desired miscibility. Highly preferred thermoplastic polymers are those which have a low degree of crystallization, a low degree of hydrogen-bonding, low solubility in water, and high solubility in organic solvents.

~~Thermoset polymer compositions~~

The composition of the invention may as well be a liquid formulation of a thermosetting oligomeric pre-polymer or copolymer which is capable of cross-linking or hardening to provide a microporous gelatinous or solid matrix suitable for use as an implant in an animal, including a human. The thermosetting pre-polymers and resulting cross-linked polymers and copolymers are biocompatible, and biodegradable and/or bioerodible.

The pre-polymers are preferably low molecular weight polymers or oligomers having end functional groups that are reactive with acryloyl chloride to produce acrylic ester-terminated pre-polymers. Acrylic pre-polymers for use in the compositions may be synthesized according to a variety of methods including, but not limited to, reaction of a carboxylic acid, such as acrylic or

methacrylic acid, with an alcohol; reaction of a carboxylic acid ester, such as methyl acrylate or methyl methacrylate, with an alcohol by transesterification; and reaction of an isocyanatoalkyl acrylate, such as isocyanatoethyl methacrylate, with an alcohol.

The thermosetting prepolymers are also short chain polyol derivatives of the thermoplastic polymers described herein. The polyol terminated derivatives are converted to acrylic ester terminated prepolymers by any suitable method. Examples are short chain polyol derivatives of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein.

A ~~preferred~~ polymer matrix and implant prepared with thermosetting prepolymers is composed of poly(DL-lactide-co-caprolactone) (DL-PLC). To prepare the DL-PLC polymer matrix, DL-lactide or L-lactide and .gamma.-caprolactone are co-polymerized in the presence of a multifunctional polyol initiator and a curing agent to produce hydroxy-terminated PLC prepolymers. This polyol-terminated pre-polymer is then converted to an acrylic ester-terminated pre-polymer by any suitable method, as for example, by acylation of the alcohol terminus with acryloyl chloride by means of, for example, a Schotten-Baumann technique (reaction of acyl halide with alcohol).

Optionally, a curing agent, such as a catalyst, may be added to the acrylic pre-polymer mixture to enhance cross-linking of the pre-polymers and the subsequent coagulation or solidification of the resulting polymer to form a matrix. For example, the acrylic pre-polymer, in an amount of about 5 grams, may be added to a solution of benzoyl peroxide (BP) in about 1 ml of CH_2Cl_2. Optionally, other acrylic monomers may be added to the acrylic pre-polymer mixture before adding the curing agent. The acrylic pre-polymer mixture may be cured in air at room temperature, or in a preheated vacuum oven.

Preferred catalysts for the preparation of the PLC prepolymers are basic or neutral ester-interchange (transesterification) catalysts, as for example, metallic esters of carboxylic acids containing up to 18 carbon atoms, formic, acetic, lauric, stearic, and benzoic acid. Preferred catalysts include, for example, stannous octoate and stannous chloride.

A multi-functional polyol chain initiator may be included in the thermosetting polymer compositions to vary the molecular weight and composition of the polymer. For example, a bifunctional chain initiator such as ethylene glycol, may be included to produce a bifunctional polymer, or a trifunctional initiator, such as trimethylolpropane, may be used to produce a trifunctional polymer. Further, the molecular weight of the polymer or co-polymer may be varied according to the concentration of the chain initiator in the composition. For example, a

high concentration of a bifunctional chain initiator may make available an initiator molecule for each polymer chain, while a low concentration may contain one initiator molecule for every two polymer chains.

Following the addition of the curing agent, the pre-polymer polymer mixture preferably remains in liquid form for a period of time effective to allow administration of the composition to the implant site. Thereafter, the cross-linking reaction preferably continues until a solid or gelatinous polymer matrix is produced. Accordingly, the pre-polymer mixture cures, or solidifies, in situ to form a polymer matrix which is capable of biodegradation and/or bioabsorption over time.